AL/OE-TR-1994-0067

QSAR EVALUATION OF HALON 1301 (CF_3Br) AND CF_3I

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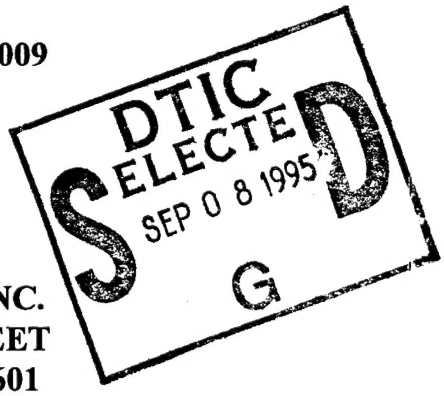

January 1994

INTERIM REPORT FOR THE PERIOD SEPTEMBER THROUGH NOVEMBER 1993

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TECHNICAL REVIEW AND APPROVAL

AL/OE-TR-1994-0067

The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

Terry A. Childress

TERRY A. CHILDRESS, Lt Col, USAF, BSC
Director, Toxicology Division
Armstrong Laboratory

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13. ABSTRACT (Maximum 200 words)

The chemical compound CF_3I is a replacement candidate for the in-flight fire extinguishing Halon 1301 (CF_3Br). One concern in choosing a suitable replacement for CF_3Br is the toxicity of the replacement candidate. Since toxicological data comparing CF_3Br and CF_3I are not available, this comparison was done using a computer model for toxic endpoints. Quantitative Structure Activity Relationship (QSAR) was performed to compare the toxicity of CF_3Br and CF_3I. These two chemicals were evaluated for rodent carcinogenicity and mouse inhalation LC_{50}. The comparisons were made using the TOPKAT computer program (Health Designs Inc., Rochester, NY). TOPKAT is a QSAR database program that can predict a variety of toxicological endpoints. The predictive capability of the TOPKAT program can be used to statistically estimate the toxicity of chemical compounds. The results of the QSAR evaluation of CF_3Br and CF_3I show that the toxicity of these compounds is not significantly different for either rodent carcinogenicity or mouse inhalation LC_{50}.

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PREFACE

This report describes the quantitative structure-activity relationship (QSAR) evaluation of bromotrifluoromethane (Halon 1301, CF_3Br) and iodotrifluoromethane (CF_3I), which was conducted by Health Designs Inc. under a subcontract to the Toxic Hazards Research Unit (THRU), ManTech Environmental Technology, Inc. The THRU is located at Wright-Patterson Air Force Base, Ohio. This work was performed under Department of the Air Force Contract No. F33615-90-C-0532 (Study No. F24). Lt Col James N. McDougal and Lt Col Terry A. Childress, respectively, served as Contract Technical Monitor for the Toxicology Division, Occupational and Environmental Health Directorate, Armstrong Laboratory. This document serves as an interim report on replacement chemicals for Halon 1301. The research described herein began in September 1993 and was completed in November 1993. Permission has been obtained from Health Designs Inc. to reproduce this report herein.

TOPKAT Toxicity Estimation Report for

ManTech Environmental Technology, Inc.

10 November, 1993

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TOPKAT Toxicity Estimation Report
for
ManTech Environmental Technology, Inc.

10 November 1993

Background

The ***TOPKAT*** program predicts toxicity of a submitted chemical structure based on diligently-developed statistically significant and robust Quantitative Structure-Activity Relationship (QSAR) equations. The QSAR equations in the ***TOPKAT*** program are either linear multiple regression equations (for continuous toxicity metrics such as LD_{50}, LC_{50}, EC_{50}, MTD, LOAEL, etc.) or two-group linear discriminant functions (for dichotomous toxicity metrics such as mutagenicity, carcinogenicity, teratogenicity, biodegradability, etc.). The regression models in the ***TOPKAT*** program produce toxicity estimates in weight/weight or weight/volume units, whereas the discriminant models output the probability (between 0 and 1) that the submitted structure be associated with a positive endpoint value.

Each model in the ***TOPKAT*** program is associated with a respective data base and is developed from experimental toxicity data and numerical descriptors of molecular structures of single organic compounds in the data base. For each model, there is a set each of significant and non-significant structure descriptors. The descriptors in the former set are related to the chosen toxicity metric and influence the estimate, whereas, those in the latter set, like the significant descriptors, are important in determining if the submitted structure is within the structure space spanned by the data base compounds.

TOPKAT always outputs an estimate of the chosen toxicity metric. However, whether the predicted value is meaningful or not can only be answered by (1) ascertaining how well the submitted structure fits within the structure space spanned by the data base compounds, and (2) finding compounds in the model data base which support the predicted value. The ***TOPKAT*** program provides functions "COVER" and "SEARCH" to do so.

The "COVER" function determines the overlap of the structural features common to the submitted structure and the training set compounds. When the salient structural attributes of the submitted structure are shared by the data base compounds, the structure is said to have adequate coverage and a "moderate" confidence can be assigned. As the overlap between the structural features in the submitted structure and the modeling set decreases, an estimate tends to be less reliable.

The "SEARCH" function helps gain additional confidence in the prediction and allows display of targeted compounds from the modeling set. In the data base associated with the chosen model, if one finds compounds with those structural features which are present in the submitted structure **and** they bear similarity to the submitted structure **and** their experimental and estimated toxicity are in concordance with that predicted for the submitted structure, the confidence in the prediction is enhanced.

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TOPKAT Toxicity Estimation Report
for
ManTech Environmental Technology, Inc.

10 November 1993

Chemical ID: **MET-1**

Estimate of **Rodent Carcinogenicity** Estimate: **0.000 (non-carcinogenic)**

A. SUBSTRUCTURAL COVERAGE:

There is only one major structural feature in this molecule, a methyl-trifluoro-iodine fragment. Since this feature describes the entire structure, there are few structure-activity relationships available for study. One might consider fragments of this feature such as a trifluoro methyl group bound to some atom other than iodine, or iodo-halo-methanes, for example.

The estimate of carcinogenicity for this structure is produced from the equation's constant, i.e., there are no other features common to the input structure and the descriptors in the equation. A check of the descriptors which did not enter the equation for statistical reasons, but are represented in database compounds indicates that there are several halo-methanes.

B. SUPPORT COMPOUNDS

Although there are no trifluoro methanes in this module's database there are several examples of halo-methanes. One of these, shown with the estimate report, contains a fluorine atom and is a correctly classified non-carcinogen. A compound structurally similar to this monofluoro-methane, carbon tetrachloride, is a correctly classified carcinogen. Another database compound, Iodoform, is also presented with the estimate report and it too is a correctly classified non-carcinogen and a compound structurally similar to this triiodo-methane, chloroform, is a correctly classified carcinogen. Therefore, there is some evidence that the presence of a fluorine or iodine atom in place of a chlorine in a halo-methane molecule "detoxifies" the endpoint and the *TOPKAT* program is sensitive to distinguishing this phenomenon.

C. SUMMARY

The database contains several halo-methane compounds and there is some evidence that the presence of a fluorine or iodine atom in place of a chlorine in a halo-methane molecule produces a non-carcinogenic result; however, since this evidence is not statistically significant, i.e, there was not sufficient data to model this observation, and since there are no trifluoro-halomethanes in this database, low confidence has been assigned to the estimate.

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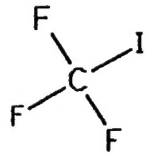
ID: MET-1 MF: C-F3-I



ESTIMATE FOR POSITIVE ENDPOINT = 0.000

Carcinogenesis Model (Version 2.0)

	Cross Product
Constant Term	-23.101
	-23.101

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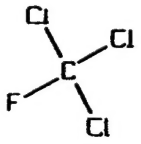
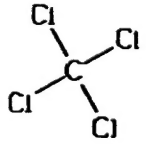
Structures Retrieved From Search of Database
For Carcinogenesis Model (Version 2.0)

NAME: TRICHLOROFLUOROMETHANE ID: 75-69-4 ACTUAL: NEG USED: Yes
REF: TABLE 7 /RPT 106 NCI/NTP PRED: 0.002 NEG



Structure Number 1

NAME: CARBON TETRACHLORIDE ID: 56-23-5 ACTUAL: POS USED: Yes
REF: TABLE 1 IARC PRED: 1.000 POS



Structure Number 2

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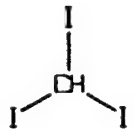
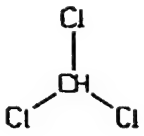
NAME: IODOFORM ID: 75-47-8 ACTUAL: NEG USED: Yes
REF: TABLE 7 /RPT 110 NCI/NTP PRED: 0.000 NEG



Structure Number 3

NAME: CHLOROFORM ID: 67-66-3 ACTUAL: POS USED: Yes
REF: TABLE 1 /RPT N/A NCI/NTP PRED: 1.000 POS



Structure Number 4

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TOPKAT Toxicity Estimation Report
for
ManTech Environmental Technology, Inc.

10 November 1993

Chemical ID: **MET-1**

Estimate of **Mouse Inhalation LC_{50}** Estimate: **209.1 gm/m^3**

A. SUBSTRUCTURAL COVERAGE:

There is only one major structural feature in this molecule, a methyl-trifluoro-iodine fragment. Since this feature describes the entire structure, there are few structure-activity relationships available for study. One might consider fragments of this feature such as a trifluoro methyl group bound to some atom other than iodine, or iodo-halo-methanes, for example. A warning was generated by the *TOPKAT* program for the estimate of mouse inhalation LC_{50} regarding the presence of only two compounds containing an iodine atom, i.e., the presence of this atom is statistically non-significant for modeling structure activity relationships in this endpoint.

As seen in the cross-products table, the estimate of mouse inhalation LC_{50} for this structure is produced from two topological features. These describe the shape and branchedness of the structure. There are several halo-methanes in this database and although none has a trifluoro-halo fragment these topological descriptors are sensitive to the connections of different halogen atoms.

B. SUPPORT COMPOUNDS

Although there are no trifluoro-methanes in this database, it is the topological features which are important for estimating the endpoint in this model. Two tetrahalo-methanes from this module's database are presented with the estimate report. They are all non-toxic and their LC_{50} values are estimated within a factor of two, indicating good model performance for this class of chemicals. Both of these compounds are chloro-fluoro-methanes, while the input structure is an iodo-fluoro-methane. This structural difference is picked-up by the topological descriptors and is reflected in the estimates of mouse inhalation LC_{50} for these molecules.

One of the two iodine-containing compounds is also presented with the estimate report. Although it is a more fluorinated compound, it does bear some structural similarity to the input structure and its actual and estimated mouse inhalation LC_{50} values are in range with the estimate for the input structure.

C. SUMMARY

The estimate is based on topological descriptors, and the input structure is topologically related to three database compounds, whose estimated mouse inhalation LC_{50} values are within experimental error of their assayed value. Because of this, and the good model performance on the other fluorinated compound which bears some structural similarity to the input structure, a moderate level of confidence has been assigned to this estimate.

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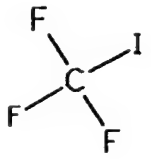
ID: MET-1 MF: C-F3-I



Est of Lc50 (2.00 Hr) = 209.1 gm/m3 or 2.5 pph

Overall Mouse Inhalation Lc50 Model

	Cross Product
Constant Term	0.000
Atom Specific Kappa Index Order 1	0.449
Difference Cluster MCI Order 3	-0.934
	-0.485

Est. of Log(1/Mole Fraction*Minutes) = -0.485

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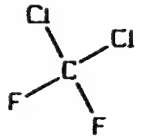
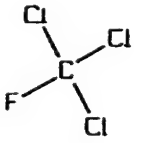
Structures Retrieved From Search of Database
For Overall Mouse Inhalation Lc50 Model

NAME: DICHLORODIFLUOROMETHANE ID: 75-71-8 ACTUAL: -1.36 76 pph 30M
USED: Yes REF: EJTXAZ 9,385,76 PRED: -0.426 481.9 gm/m3 8.9 pph
ID2: PA8200000



Structure Number 1

NAME: TRICHLOROFLUOROMETHANE ID: 75-69-4 ACTUAL: -.477 10 pph 30M
USED: Yes REF: EJTXAZ 9,385,76 PRED: 0.150 135.7 gm/m3 2.4 pph
ID2: PB6125000



Structure Number 2

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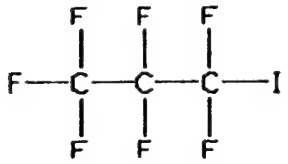
NAME: HEPTAFLUORO-1-IODO-PROPANE ID: 754-34-7
ACTUAL: -.588 404 gm/m3 2H USED: Yes REF: 85GMAT -,76,82
PRED: -0.225 171.8 gm/m3 1.4 pph ID2: TZ3930000



Structure Number 3

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TOPKAT Toxicity Estimation Report
for
ManTech Environmental Technology, Inc.

10 November 1993

Chemical ID: **MET-2**

Estimate of **Rodent Carcinogenicity** Estimate: **0.000 (non-carcinogenic)**

A. SUBSTRUCTURAL COVERAGE:

There is only one major structural feature in this molecule, a methyl-trifluoro-bromine fragment. Since this feature describes the entire structure, there are few structure-activity relationships available for study. One might consider fragments of this feature such as a trifluoro methyl group bound to some atom other than bromine, or bromo-halo-methanes, for example.

The estimate of carcinogenicity for this structure is produced from the equation's constant, i.e., there are no other features common to the input structure and the descriptors in the equation. A check of the descriptors which did not enter the equation for statistical reasons, but are represented in database compounds indicates that there are several halo-methanes.

B. SUPPORT COMPOUNDS

Although there are no trifluoro methanes in this module's database there are several examples of halo-methanes. One of these, shown with the estimate report, contains a fluorine atom and is a correctly classified non-carcinogen. A compound structurally similar to this monofluoro-methane, carbon tetrachloride, is a correctly classified carcinogen; therefore, there is some evidence that the presence of a fluorine atom in place of a chlorine in a tetrahalo-methane molecule "detoxifies" the endpoint and the *TOPKAT* program is sensitive to distinguishing this phenomenon.

However, there are only two bromo-methanes, both of which were set aside during the development of this model for statistical reasons, i.e., the model does not perform well on predicting their carcinogenicity endpoints. This suggests that the model may not perform well on estimating carcinogenicity for input structures of a similar chemical class.

C. SUMMARY

The database contains several halo-methane compounds and there is some evidence that the presence of a fluorine or iodine atom in place of a chlorine in a halo-methane molecule is associated with non-carcinogenicity; however, since this evidence is not statistically significant, i.e., there were not sufficient data to model this observation, and since there are no trifluoro-halomethanes in this database, and the model does not perform well on predicting the carcinogenicity of the two bromo-methanes in this database, low confidence has been assigned to the estimate.

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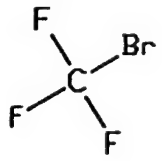
ID: MET-2 MF: C-Br-F3



ESTIMATE FOR POSITIVE ENDPOINT = 0.000

Carcinogenesis Model (Version 2.0)

	Cross Product
Constant Term	-23.101
	-23.101

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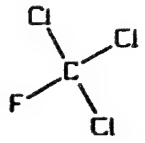
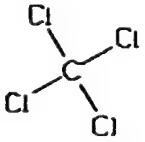
Structures Retrieved From Search of Database
For Carcinogenesis Model (Version 2.0)

NAME: TRICHLOROFLUOROMETHANE ID: 75-69-4 ACTUAL: NEG USED: Yes
REF: TABLE 7 /RPT 106 NCI/NTP PRED: 0.002 NEG



Structure Number 1

NAME: CARBON TETRACHLORIDE ID: 56-23-5 ACTUAL: POS USED: Yes
REF: TABLE 1 IARC PRED: 1.000 POS



Structure Number 2

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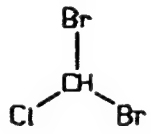
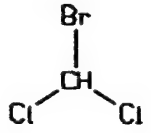
NAME: CHLORODIBROMOMETHANE ID: 124-48-1 ACTUAL: POS
USED: No, Statistical Outlier REF: TABLE 5 /RPT 282 NCI/NTP



Structure Number 3

NAME: BROMODICHLOROMETHANE ID: 75-27-4 ACTUAL: POS
USED: No, Statistical Outlier REF: TABLE 1 /RPT 321 NCI/NTP



Structure Number 4

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TOPKAT Toxicity Estimation Report
for
ManTech Environmental Technology, Inc.

10 November 1993

Chemical ID: **MET-2**

Estimate of **Mouse Inhalation LC_{50}** Estimate: **201.1 gm/m^3**

A. SUBSTRUCTURAL COVERAGE:

There is only one major structural feature in this molecule, a methyl-trifluoro-bromine fragment. Since this feature describes the entire structure, there are few structure-activity relationships available for study. One might consider fragments of this feature such as a trifluoro methyl group bound to some atom other than bromine, or bromo-halo-methanes, for example.

As seen in the cross-products table, the estimate of mouse inhalation LC_{50} for this structure is produced from two topological features. These describe the shape and branchedness of the structure. There are several halo-methanes in this database and although none has a trifluoro-halo fragment these topological descriptors are sensitive to the connections of different halogen atoms.

B. SUPPORT COMPOUNDS

Although there are no trifluoro-methanes in this database, it is the topological features which are important for estimating the endpoint in this model. Two tetrahalo-methanes from this module's database are presented with the estimate report. They are all non-toxic and their LC_{50} values are estimated within a factor of two, indicating good model performance for this class of chemicals. Both of these compounds are chloro-fluoro-methanes, while the input structure is a bromo-fluoro-methane. This structural difference is picked-up by the topological descriptors and is reflected in the estimates of mouse inhalation LC_{50} for these molecules.

There is only one database compound consisting of a bromo-methane. It is also presented with the estimate report and is correctly predicted to be relatively non-toxic. This compound is not as topologically similar to the input structure as the two aforementioned database compounds, since it is a monohalo-methane; however, in support of a similar response to the endpoint given a bromine atom versus a chlorine atom, chloromethane is presented with the estimate report. This compound is topologically similar to bromomethane and the experimental and predicted mouse inhalation LC_{50} values for these two monohalo-methanes are comparable.

C. SUMMARY

The estimate is based on topological descriptors, and the input structure is topologically related to two database compounds, whose estimated mouse inhalation LC_{50} values are within experimental error of their assayed values. Because of this, and since there is some evidence that bromo-methanes and chloro-methanes behave similarly and are well predicted by the ***TOPKAT*** program, a moderate level of confidence has been assigned to this estimate.

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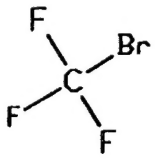
ID: MET-2 MF: C-Br-F3



Est of Lc50 (2.00 Hr) = 201.1 gm/m3 or 3.2 pph

Overall Mouse Inhalation Lc50 Model

	Cross Product
Constant Term	0.000
Atom Specific Kappa Index Order 1	0.430
Difference Cluster MCI Order 3	-1.014
	-0.584

Est. of Log(1/Mole Fraction*Minutes) = -0.584

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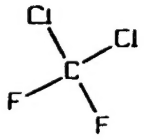
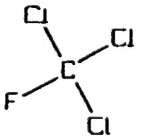
Structures Retrieved From Search of Database
For Overall Mouse Inhalation Lc50 Model

NAME: DICHLORODIFLUOROMETHANE ID: 75-71-8 ACTUAL: -1.36 76 pph 30M
USED: Yes REF: EJTXAZ 9,385,76 PRED: -0.426 481.9 gm/m3 8.9 pph
ID2: PA8200000



Structure Number 1

NAME: TRICHLOROFLUOROMETHANE ID: 75-69-4 ACTUAL: -.477 10 pph 30M
USED: Yes REF: EJTXAZ 9,385,76 PRED: 0.150 135.7 gm/m3 2.4 pph
ID2: PB6125000



Structure Number 2

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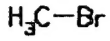
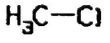
NAME: BROMOMETHANE ID: 74-83-9 ACTUAL: 1.323 1.54 gm/m3 2H
USED: Yes REF: 85GMAT -,81,82 PRED: 0.226 19.3 gm/m3 4951.7 ppm
ID2: PA4900000



Structure Number 3

NAME: CHLOROMETHANE ID: 74-87-3 ACTUAL: -.121 3146 ppm 7H
USED: Yes REF: NIHBAZ 191,1,49 PRED: 0.207 3.1 gm/m3 1479.1 ppm
ID2: PA6300000



Structure Number 4

U. S. Government Printing Office 1995 650-075/00082

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